REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Applicants sincerely thank the Examiner for holding a personal interview with Applicant's representative on October 3, 2007 and speaking with Applicant's representative over the telephone about this case on October 10, 2007. Applicants have incorporated Examiner's kind suggestions into the claims and remarks.

I. Claim Status and Amendments

Claims 1-24 were pending in this application when last examined.

Claims 1-24 were examined on the merits and rejected.

Claims 6, 8-9, 13-15 and 19-24 are amended to properly recite method claims under US practice, as suggested by the Examiner. Support for these amendments can be found in the claims as filed. Further, support for treatment of a mammal can be found on page 32, lines 8-10, of the specification as filed. The claims have also been amended to delete reference to "prophylaxis", as suggested by the Examiner.

Claims 7 and 16-18 are cancelled. Applicants reserve the right to file a continuation or divisional application on any cancelled subject matter.

No new matter has been added.

II. Foreign Priority

In item 12 on page 1 of the Office Action, acknowledgement of foreign priority under 35 U.S.C. § 119(a)-(d) or (f) was not indicated. Applicants respectfully request the Examiner to indicate the claim for foreign priority by checking the appropriate boxes in item 12 of the next Office Action.

III. Indefiniteness Rejection

On page 2 of the Office Action, claims 6-9 and 13-24 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the recitation of preamble language that can be read as either a method of treating or as a pharmaceutical composition. Page 2 further indicates such claims are being examined as method claims.

Claims 6, 8-9, 13-15 and 19-24 are amended to recite methods in conformance with US practice. Such amendments were suggested by the Examiner in the last Office Action on page 2 and during the above-noted interview with Applicant's representative. Claims 7 and 16-18 are cancelled as suggested by the Examiner during the interview. Applicants therefore respectfully suggest that this rejection, as applied to the remaining amended claims, is untenable and should be withdrawn.

IV. Obviousness Rejections

A. EP 0526840 and US 5,281,610

On pages 3 and 4, claims 1-24 were rejected under 35 U.S.C. § 103(a) as obvious over EP 0 526 840 or Suzuki et al. (US 5,281,610). Applicants respectfully traverse this rejection, as applied to the remaining amended claims, for the following reasons.

1. Structural differences between the claimed compounds and Suzuki et al. compounds

The claimed compounds have a core skeleton (pyrazolo[4,3-c] [1,8]naphthyridin-4 (5H)-one) and are molecules wherein the substituent at the 3-position is a group having an unsubstituted or substituted phenyl, pyridyl, 1-oxypyridyl or thienyl group via 1 to 3 methylene chains. As disclosed in the specification on page 5 and on page 12, lines 10-21, said substituent at the 3-position is a distinctive feature for acquisition of PDE IV inhibitory activity.

In contrast, although the Suzuki et al. compounds have the same core, the substituent at position 3 (R^2) is hydrogen, lower alkyl, thienyl, substituted or unsubstituted aryl, hydroxyl or

amino (see claim 1 of US '610) without a 1 to 3 methylene chain. Thus, Suzuki et al. teaches a different chemical structure than the claimed invention.

2. Advantages of the claimed invention

The claimed compounds exhibit excellent potent inhibitory action toward PDE IV and predominantly inhibit PDE IV in airway smooth muscle cells and inflammatory cells. This elevates cAMP levels in said cells, causing relaxation of airway smooth muscle and simultaneous suppression of inflammatory cell activation. Further, the claimed invention allows for the production of exceedingly pharmacologically-effective and safe anti-asthmatic agents and valuable prophylactic and/or therapeutic agents for the treatment of COPD (see page 11, lines 9-23, of the specification). These advantageous effects are supported by the disclosures in Assay Example 1. See "PDE IV Inhibition" on pages 33-35 of the specification.

In contrast, although the compounds taught in Suzuki et al. have anti-inflammatory, immunosuppressive, broncho-dilatory and hair growth-stimulative effects, and relax guinea pig tracheae (see "(2) Passive Schultz-Dale (S-D) Reaction" in column 13, lines 20-43 and Table 3 of US '610), there is no description of PDE IV inhibitory effects.

Thus, Suzuki et al. fails to provide motivation sufficient to lead to the present invention wherein PDE IV inhibitory actions are claimed on the basis of biological mechanism and in vitro data. A person of skill in the art in view of Suzuki et al. would not optimize PDE IV inhibition because the compounds of Suzuki et al. are not indicated as having PDE IV inhibitory activity.

3. Differences in structure and biological effects between the claimed compounds and the Suzuki et al. compounds

At the top of page 4 of the Office Action, the Office contends that the only difference in the structure between the compounds taught in Suzuki et al. and the claimed compounds is the presence of $(CH_2)_m$ linker in the instant claims. Therefore, the Office contends that one of skill in the art in the business of making new drugs would have been motivated to make the indicated

minor change because the close structural similarity would have motivated someone skilled in the art to modify the prior art to obtain the compounds of the invention and also expect them to retain anti-asthmatic properties.

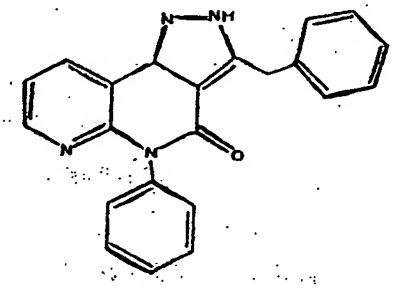
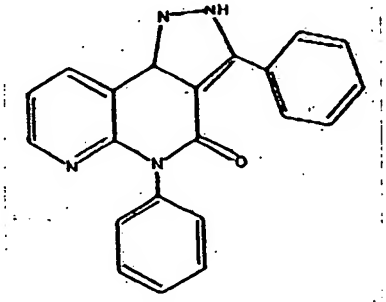
However, as pointed out above, the claimed compounds not only have the core skeleton, "pyrazolo [4,3-c] [1-8] naphthyridin-4(5H)-one", but also the substituent at the 3-position is a group having an unsubstituted or substituted phenyl, pyridyl, 1-oxypyridyl or thienyl group via 1 to 3 methylene chains.

The important feature of the claimed compounds resides in the substituent at position 3 bonded through a methylene linker on the core skeleton. In other words, the present invention is based on the finding that the unique chemical structure with such a methylene linker on the pyrazolo ring successfully provides an unexpected increase in PDE IV inhibition.

In order to demonstrate the advantages of the claimed compounds, a comparison study was performed between a claimed compound (Example No. 9 on page 68 of the specification; hereinafter referred to as the "inventive compound") and US '610 Compound 1, which is a molecule derived by removal of methylene from the inventive compound, (3,5-diphenyl-1H-pyrazolo [4,3-c] [1-8] naphthyridin-4(5H)-one; hereinafter referred to as the "US '610 compound") for their PDE IV inhibitory efficacies according to assay methods disclosed in the present specification. The results are shown in Table 1 below.

Table 1

PDE IV INHIBITION COMPARISON BETWEEN
THE INVENTIVE COMPOUND AND THE US '610 COMPOUND

	The Inventive Compound	The US '610 Compound
Chemical Formula		
PDE IV Inhibition (IC_{50})	0.084 μM	0.25 μM

As apparent from Table 1, the PDE IV inhibitory efficacy (IC_{50} = 0.084μM) of the inventive compound is about 3 times higher than the PDE IV inhibitory efficacy (IC_{50} = 0.25μM) of the US '610 compound.

Thus, the presence or absence of methylene greatly affects PDE IV inhibition activity. This study demonstrates the unexpectedly superior PDE IV inhibition activity of the inventive compound. This augmentation in PDE IV inhibition would not have been expected by a person skilled in the art.

Furthermore, one of the unique features of the claimed invention is that the inventive compounds reduce *in vivo* adverse drug reactions.

As shown in Assay Example 4 (on page 39 of the specification), the claimed compounds only slightly inhibit drug-metabolizing enzymes CYP2D6 and CYP3A4. The inhibition (IC_{50}) of CYP2D6 and CYP3A4 is >10 μM and 8.5 μM, respectively, for the claimed compound in

Example No. 9. This data indicates that the claimed compounds do not strongly inhibit drug-metabolizing enzymes. This suggests that after the instant compounds are ingested they will be rapidly metabolized by drug-metabolizing enzymes, reducing drug side-effects. Suzuki et al. neither suggests nor discloses such effects and advantages.

Therefore, Suzuki et al. does not (1) teach the claimed compounds with a methylene linker, (2) suggest the claimed compounds with PDE IV inhibitory activity, (3) suggest the unexpectedly superior PDE IV inhibition of the claimed compounds or (4) suggest the reduced inhibition of drug metabolizing enzymes of the claimed compounds. From the foregoing remarks, it is clear that Suzuki et al. neither teaches nor suggests the claimed invention.

B. JP 6-100561 and US 5,281,610

On pages 4-6 of the Office Action, claims 1-24 were rejected under 35 U.S.C. § 103(a) as unpatentable over JP 06-100561 in view of US '610. Applicants respectfully traverse this rejection, as applied to the amended claims, for the following reasons.

1. Structural differences between the claimed compounds and the JP 6-100561 A (JP '561) compounds (especially Example 100 Compound).

The claimed compounds have the core skeleton pyrazolo ([4,3-c] [1-8] naphthyridin-4(5H)-one) and are molecules wherein the substituent at the 3-position is a group having an unsubstituted or substituted phenyl, pyridyl, 1-oxypyridyl or thienyl group via 1 to 3 methylene chains. As discussed above, said substituent at the 3-position is a distinctive feature for PDE IV inhibitory actions.

In contrast, although the JP '561 compounds have the same core, the substituent at position 3, (R^4) is hydrogen, lower alkanoyloxy, hydroxy, lower alkoxy or NR^5R^6 (see, claim 1 of JP '561), which is different in chemical structure from those of the claimed invention.

Compound 100 (pointed out by the Office), wherein benzyl is substituted at position 2 on the pyrazolo ring, is clearly distinctive in chemical structure, because benzyl is positioned at position 3 on the pyrazolo ring of the instant compounds. Furthermore, due to the difference in substituent benzyl between the 2-position and the 3-position, the core pyrazolo ring differs from each other in the position of a double bond. Thus, the core skeleton of the instant compounds is distinctive from that of "Compound 100".

2. Advantageous effects of the present invention

The claimed compounds exhibit excellent potent inhibitory action toward PDE IV and predominantly inhibit PDE IV in airway smooth muscle cells and inflammatory cells. This elevates cAMP levels in said cells, causing relaxation of airway smooth muscle and simultaneous suppression of inflammatory cell activation. Further, the claimed invention allows for the production of exceedingly pharmacologically-effective and safe anti-asthmatic agents and valuable prophylactic and/or therapeutic agents for the treatment of COPD (see page 11, lines 9-23, of the specification). These advantageous effects are supported by the disclosures in Assay Example 1. See "PDE IV Inhibition" on pages 33-35 of the specification.

In contrast, although JP '561 mentions that the discussed compounds have excellent anti-inflammatory, immunoregulating, analgesic or antipyretic actions, and are useful as an immunoregulating, anti-inflammatory, analgesic or antipyretic agent for curing or preventing chronic arthrorheumatism, nephritis, psoriasis, systemic lupus erythematosus, or lumbago, there is no description explaining the mechanism by which such actions and effects are exerted. Furthermore, no in vitro data (assay examples) are disclosed in JP '561 demonstrating such actions or effects. Therefore, the mechanism of pharmaceutical action and efficacy of the JP '561 compounds are entirely unknown. Thus, it is impossible to compare the JP '561 compounds with the present invention.

From the foregoing, JP '561 has a defect in disclosing the mechanism and supporting data for such pharmaceutical actions and effects as anti-inflammatory action, though anti-inflammatory, immunoregulating, analgesic and antipyretic actions are described therein.

JP '561 teaches a compound with a similar side chain but a different core structure and fails to disclose the mechanism by which the pharmaceutical effects occur. The presence of a substituent at a different position in the compounds of JP '561 does not teach or suggest the claimed invention wherein the pharmaceutical and biological actions and effects are claimed on the basis of uncovered PDE IV inhibitory activity. Thus, a person of skill in the art in light of JP '561 would not be taught or suggested the claimed compounds since such have a different core structure in relation to the substituents and a person of skill in the art would not be motivated to optimize PDE IV inhibition since JP '561 does not teach pharmaceutical activity is dependent on PDE IV inhibition.

Applicants further note, as discussed above, the claimed invention exhibits unexpectedly superior PDE IV inhibitory activity and decreased drug metabolizing enzyme inhibition. JP '561 neither teaches nor suggests such properties of the claimed compounds.

Further, as noted above, Suzuki et al. does not (1) teach the claimed compounds with a methylene linker, (2) suggest the claimed compounds with PDE IV inhibitory activity, (3) suggest the unexpectedly superior PDE IV inhibition of the claimed compounds or (4) suggest the unexpectedly reduced inhibition of drug metabolizing enzymes of the claimed compounds. Thus, it is clear that Suzuki et al. neither teaches nor suggests the claimed invention and further that the present invention exerts significantly superior biological and pharmaceutical actions.

Since, as noted above, neither Suzuki et al. nor the combination of JP '561 with Suzuki et al. teaches or suggests the claimed invention; Applicants suggest this rejection is untenable and should be withdrawn.

V. Enablement Rejection

On pages 6-10, claims 1-24 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is only enabling for some assay data and some asthmatic response, and not for treating or the "prophylaxis" of any condition related to phosphodiesterase IV.

Applicants respectfully traverse this rejection, as applied to the remaining amended claims, for the following reasons. Applicants again thank the Examiner for holding a personal interview with Applicant's representative to discuss this enablement rejection. Examiner's kind suggestions have been incorporated into this reply.

Applicants have amended the claims to delete the term prophylaxis. Applicants have further deleted claims directed toward treating diseases and conditions directly or indirectly related to phosphodiesterase IV.

Applicants further note that Table I on page 34 of the specification lists 19 compounds encompassed by the claims and indicates such compounds inhibit PDE IV *in vitro*. Applicants also note that pages 35-43 of the specification present *in vivo* data showing two of the compounds listed in Table I are effective for inhibiting antigen induced asthmatic response, TNF-α production, Lung eosinophil infiltration and lung neutrophil infiltration. Such pathologies are associated with the disease causing mechanisms for bronchial asthma including chronic bronchial asthma and atopic asthma; acute bronchitis; chronic bronchitis; asthmatic bronchitis; pneumonic diseases; pulmonary emphysema; chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). Applicants submit that a person of skill in the art would consider all the compounds listed in Table I, which are shown to have PDE IV inhibitory activity, to also exhibit the *in vivo* activities indicated on pages 35-43 of the specification.

Applicants have also attached the following three documents, with English Abstracts and English translations of the relevant portions, establishing *in vivo* activities of a number of compounds with PDE IV inhibitory activity:

(1) JP Hei-10875, A (Appendix 1)

In Example 5 of this reference (English translation enclosed), the inhibitory effects on airway constriction of PDE IV inhibitors were verified in a protocol similar to that in Assay Example 2 of the present Specification.

(2) JP Hei 11-106385, A (Appendix 2) (corresponding to USP Nos. 6,297,248 & 6,541,480)

In Paragraph [0044] of this reference (English translation enclosed), inhibitory activities on TNF-α production of PDE IV inhibitors were assayed in a protocol similar to that in Assay Example 3 of the present Specification.

(3) WO 99/38867, A (Appendix 3) (corresponding to USP No. 6,331,548)

On page 30 of this reference (English translation enclosed), inhibitory activities on TNF-α production of PDE IV inhibitors were assayed in a protocol similar to that in Assay Example 3 of the present Specification.

Applicants therefore submit that because (1) numerous compounds of the claimed invention are confirmed to have PDE IV inhibitory activity, (2) some of these compounds also have numerous *in vivo* activities and (3) the PDE IV inhibitors in the cited references have *in vivo* activity, a person of skill in the art would understand that the claimed compounds and methods of treatment are enabled.

Therefore, Applicants submit that the above-noted enablement rejection is untenable as applied to claims 1-5 and 10-12 as such claims recite compounds or pharmaceutical compositions that the above-noted data indicates are useful for PDE IV inhibition and to treat disease *in vivo*. Further, the above-noted rejection is untenable as applied to method claims 6, 8-9, 13-15 and 19-24 because, as noted above, a person of skill in the art would understand these methods to be enabled for the claimed compounds.

Applicants therefore suggest that this rejection, as applied to the remaining amended claims, is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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